PB88-161963

Health and Environmental Effects Profile for Hydrazine and Hydrazine Sulfate

(U.S.) Environmental Protection Agency
Cincinnati, OH

Jan 84

U.S. Department of Commerce
National Technical Information Service

TECHNICAL REPORT DATA
(Please read Instructions on the reverse before completing)

1. REPORT NO. EPA/600/X-84/332	2.
3. RECIPIENT'S ACCESSION NO. PB8 161963/AS	
4. TITLE AND SUBTITLE Health and Environmental Effects Profile for Hydrazine and Hydrazine Sulfate	5. REPORT DATE January 1984
	6. PERFORMING ORGANIZATION CODE
7. AUTHOR(S)	8. PERFORMING ORGANIZATION REPORT NO.
9. PERFORMING ORGANIZATION NAME AND ADDRESS	10. PROGRAM ELEMENT NO.
	11. CONTRACT/GRANT NO.
12. SPONSORING AGENCY NAME AND ADDRESS Environmental Criteria and Assessment Office Office of Research and Development U.S. Environmental Protection Agency Cincinnati, OH 45268	13. TYPE OF REPORT AND PERIOD COVERED
	14. SPONSORING AGENCY CODE EPA/600/22
15 SUPPLEMENTARY NOTES	

16. ABSTRACT

The Health and Environmental Effects Profile for hydrazine and hydrazine sulfate was prepared by the Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH for the Office of Solid Waste to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA). Both published literature and information obtained from Agency program office files were evaluated as they pertained to potential human health, aquatic life and environmental effects of hazardous waste constituents.

Quantitative estimates have been presented provided sufficient data are available. Existing data are insufficient to determine an Acceptable Daily Intake (ADI) or a carcinogenic potency factor for hydrazine.

Hydrazine sulfate has been evaluated as a carcinogen. The human carcinogen potency factor (q_1^*) for hydrazine sulfate is 3.0 $(mg/kg\ bw/day)^{-1}$ for oral exposure.

17. KEY WORDS AND DOCUMENT ANALYSIS

a. DESCRIPTORS	b. IDENTIFIERS/OPEN ENDED TERMS	c. COSATI Field/Group

18. DISTRIBUTION STATEMENT Public	19. SECURITY CLASS (This Report) Unclassified	21. NO. OF PAGES 66
	20. SECURITY CLASS (This page) Unclassified	22. PRICE PC 14.95/MF 6.95

EPA Form 2220-1 (Rev. 4-77) PREVIOUS EDITION IS OBSOLETE

PB88-161963

EPA/600/X-84/332
January 1984

HEALTH AND ENVIRONMENTAL EFFECTS PROFILE FOR HYDRAZINE AND HYDRAZINE SULFATE

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REPRODUCED BY
U.S. DEPARTMENT OF COMMERCE
NATIONAL TECHNICAL
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SPRINGFIELD, VA. 22161

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PREFACE

Health and Environmental Effects Profiles (HEEPs) are prepared for the Office of Solid Waste by the Office of Health and Environmental Assessment. The HEEPs are intended to support listings of hazardous constituents of a wide range of waste streams under Section 3001 of the Resource Conservation and Recovery Act (RCRA). Both published literature and information obtained from Agency program office files are evaluated as they pertain to potential human health, aquatic life and environmental effects of hazardous waste constituents.

Quantitative estimates are presented provided sufficient data are available. For systemic toxicants, these include, Acceptable Daily Intakes (ADIs) for chronic exposures. An ADI is defined as the amount of a chemical to which humans can be exposed on a daily basis over an extended period of time (usually a lifetime) without suffering a deleterious effect. In the case of suspected carcinogens, ADIs are not estimated in this document series. Instead, a carcinogenic potency factor or q_1^* is provided. These potency estimates are derived for both oral and inhalation exposures where possible. In addition, unit risk estimates for air and drinking water are presented based on inhalation and oral data, respectively.

The first draft of this document was prepared by Syracuse Research Corporation under EPA Contract No. 68-03-3228. The document was subsequently revised after reviews by staff within the Office of Health and Environmental Assessment: Carcinogen Assessment Group, Reproductive Effects Assessment Group, Exposure Assessment Group, and the Environmental Criteria and Assessment Office in Cincinnati.

The HEEPs will become part of the EPA RCRA docket.

ACKNOWLEDGEMENTS

The initial draft of this report was prepared by Syracuse Research Corporation under Contract No. 68-03-3228 for U.S. EPA's Office of Health and Environmental Assessment, Environmental Criteria and Assessment Office, Cincinnati, OH. Dr. Christopher DeRosa was the Technical Project Monitor and Helen Ball was the Project Officer. The final documents in this series were prepared for the Office of Solid Waste, Washington, DC.

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LIST OF ABBREVIATIONS

BSP	Bromsulfalein
DNA	Deoxyribonucleic acid
i.p.	Intraperitoneal
LC_{50}	Concentration lethal to 50% of recipients (and all other subscripted dosage levels)
LT_{100}	Time lethal to 100% of recipients
ppm	Parts per million
STEL	Short-term exposure limit
TLV	Threshold limit value
TWA	Time-weighted average

1. INTRODUCTION

1.1. STRUCTURE AND CAS NUMBER

The synonyms, structures, molecular formulae, molecular weights and Chemical Abstract Services (CAS) registry numbers for hydrazine and hydrazine sulfate are listed below:

	Hydrazine	Hydrazine Sulfate
Synonyms	diamine, diamide sulfate	diamine sulfate, diamidogen
Structure	H_2N-NH_2	$H_2N-NH_2 \cdot H_2SO_4$
Molecular formula	H_4N_2	$H_6N_2O_4S$
Molecular weight	32.05	130.12
CAS number	302-01-2	10034-93-2

1.2. PHYSICAL AND CHEMICAL PROPERTIES

Hydrazine is a colorless, mobile, fuming and hygroscopic liquid with an ammonical odor (Schiessl, 1980). Hydrazine sulfate is a white crystalline powder. Chemically, hydrazine is a very strong reducing agent; a severe explosion hazard exists when it is exposed to or reacted with oxidizing materials.

Some of the physical properties of hydrazine and hydrazine sulfate are summarized below (Schiessl, 1980; IARC, 1973):

	Hydrazine	Hydrazine Sulfate
Boiling point	113.0-113.5°C	not located
Melting point	2.0°C	254°C
Density (25°C)	1.0045 g/ml	1.37 (sp.gr.)
Vapor pressure (20°C) (25°C)	10.4 mm Hg 14.4 mm Hg	not located

Solubility	miscible with water and other polar solvents; slightly miscible with hydrocarbons and halogenated hydrocarbons	3.4 g/100 g water at 25°C
Log octanol water partition coefficient	0.08 (calculated) (Hansch and Leo, 1981)	not located

1.3. PRODUCTION DATA

The production of hydrazine has been estimated as follows:

Year	Millions of Pounds	Reference
1982	20.0	Chemical and Engineering News, 1982
1977	18.6	Schiessl, 1980
1964	15.0	Raphaelian, 1966

Hydrazine production in 1982 was estimated to be as much as 40% lower than in 1981, due to the economic recession in vital industries (Chemical and Engineering News, 1982). It was further estimated from 1982 data that hydrazine production will grow at an annual rate of 8-10% through 1987. Hydrazine is currently produced by Olin Corp. (Lake Charles, LA), Mobay Chemical (Cedar Bayou, TX) and Fairmount Chemical (Newark, NJ) (SRI, 1983; Chemical and Engineering News, 1982; Schiessl, 1980).

Although commercially available, hydrazine sulfate is not regarded as one of the four major commercial hydrazines (i.e., hydrazine, hydrazine hydrate, monomethylhydrazine and 1,1-dimethyl hydrazine) (Schiessl, 1980). Hydrazine sulfate is produced by Fairmount Chemical (Newark, NJ) and Richardson-Vicks, Inc. (Phillipsburg, NJ) (SRI, 1983). The 1977 TSCA inventory indicates a production volume range of 100,000-1,000,000 lb/year for Fairmount Chemical.

At present, hydrazine is commercially produced in the United States either by the Raschig process or by the ketazine process (Schiessl, 1980). In the Raschig process, chloramine is formed from ammonia and hypochlorite and then reacted with excess ammonia to form hydrazine. The ketazine process is a variation of the Raschig process in which chlorine reacts continuously with dilute sodium hydroxide to form sodium hypochlorite and sodium chloride. The hypochlorite solution is reacted with aqua ammonia and acetone under slight pressure to produce ketazines and hydrazone; dimethyl ketazine is produced by the addition of more acetone and reacted with water to form hydrazine and acetone. Hydrazine sulfate is also prepared from hydrazine by treatment with sulfuric acid.

1.4. USE DATA

The major uses of hydrazine are agricultural chemicals (40%), blowing agents (33%), water treatment (15%) and aerospace propellant (5%) (Chemical and Engineering News, 1982). Approximately 80% of the hydrazine production is used in the synthesis of derivatives in agricultural chemicals, chemical blowing agents, pharmaceutical intermediates and other uses. Practically the only uses for which it is sold as a primary product are for water treatment and rocket/jet propellants (Chemical and Engineering News, 1982). Water treatment for corrosion protection is a rapidly growing use for hydrazine, particularly in boilers, hot-water heating systems and oil-well casings (Schiessl, 1980); dissolved oxidants in water is scavenged by hydrazine to a nondetectable level. Hydrazine sulfate appears to be used primarily in the manufacture of chemicals (Hawley, 1981).

2. ENVIRONMENTAL FATE AND TRANSPORT PROCESSES

Most of the information located in the available literature concerns the fate and effects of hydrazine, rather than of hydrazine sulfate. In aquatic media and soil, the pH of the medium of concern, however, determines the form hydrazine will assume; at low pH the ionized form will dominate, while at high pH, a preponderance of the free base will exist. In complex systems, the counter ion (an anion), which associates with the hydrazonium ion, will vary depending on the number and type of ions present in the solution, the strength of the associations between all the ions, the redox potential and the pH. Thus, the actual counter ion associated with a hydrazonium ion present in a system after introduction of hydrazine or hydrazine sulfate may be any of the anions already present. For example, if hydrazine sulfate is introduced into seawater, some of the hydrazonium ion present will be associated with chloride rather than sulfate. As a consequence, the form in which hydrazine is introduced into a system is irrelevant, so that the fate of hydrazine will be virtually identical to that of hydrazine sulfate. This generalization assumes that the addition of hydrazine or hydrazine sulfate does not significantly perturb the system, causing a change that would alter the course of degradation (e.g., pH change from addition of large amounts of hydrazine).

2.1. AIR

Hydrazine can be released to the atmosphere during use (e.g., residual fighter plane and rocket fuel), and from spills, leaks and venting during loading, transfer and storage. It appears that reaction with ozone and hydroxyl radicals will be the major fate of hydrazine in the atmosphere. Hydrazine does not photolyze in the solar actinic region (γ > 290 nm) (Tuazon et al., 1982).

Experiments in which 1-2.4 ppm concentrations of hydrazine were mixed with similar levels of ozone under dark conditions in a 30,000 ℓ Teflon bag provided decay data from which apparent rate constants of ~0.2 ppm^{-1} min^{-1} (21-24°C) and ~0.3 ppm^{-1} min^{-1} (44°C) were determined (Tuazon et al., 1982). From these rate constants, it was estimated that the half-life of hydrazine would range from <10 minutes during ozone pollution episodes to <2 hours in the "natural" troposphere. The major product observed in the reaction of ozone with hydrazine was H_2O_2; N_2O and NH_3 were found as minor products, but significant levels of NO_x were not formed.

When 2.85 ppm of hydrazine was mixed with air at 16% relative humidity under dark conditions without ozone in a 30,000 ℓ Teflon chamber, the approximate half-life was 5 hours (Tuazon et al., 1982). A faster half-life of ~1.8 hours was observed when 3.77 ppm hydrazine and air with a higher humidity (85%) was used. NH_3 formed during the decay but reportedly accounted for only 5-10% of the hydrazine lost, and nitrous oxide was detected as a minor product.

Hydrazine can also react rapidly with hydroxyl radicals in the atmosphere (Harris et al., 1979; Pitts et al., 1980). From data obtained under simulated atmospheric conditions in a 30,000 ℓ outdoor Teflon chamber, a temperature independent rate constant of 6.1×10^{-11} $cm^3 mol^{-1} sec^{-1}$ was determined; it was estimated that the tropospheric half-life will range from <1 hour in polluted urban atmospheres to up to 3-6 hours in unpolluted atmospheres.

Pitts et al. (1980) also found that hydrazine degraded rapidly in the presence of nitrogen oxides (NO_x). When a mixture of 1.3 ppm hydrazine and ~1 ppm NO_x (0.87 ppm NO and 0.12 ppm NO_2) were mixed in a 30,000 ℓ Teflon chamber and exposed to sunlight, essentially 100% degradation

occurred in 30 minutes. An increase in N_2O (nitrous oxide) was observed throughout the experiment. Hydrazine degradation was less rapid when similar concentrations of hydrazine and nitrogen oxides were mixed in the dark; 15% was degraded in 26 minutes and the half-life was ~2 hours. The major loss process of hydrazine in the dark experiment appeared to be its decomposition to N_2 and H_2O, with no reaction between hydrazine and NO_x.

2.2. WATER

Both dissolved oxygen and a catalyst are necessary for appreciable aqueous degradation of hydrazine (Gormley and Ford, 1973). The most effective catalyst appears to be Cu^{+2}, although Co^{+2}, Ag^{+1} and Hg^{+2} also have catalytic properties. The reaction rate is also temperature and pH dependent; degradation proceeds rapidly only in basic solutions and almost stops in acidic solution.

Slonim and Gisclard (1976) monitored the disappearance of 5 ppm hydrazine from natural (river and pond), drinking (treated city and county) and stored laboratory water. The river water contained much organic debris and caused the most rapid disappearance of hydrazine; 30, 16 and 1% of the original concentration was present after 1 hour, 1 and 2 days, respectively. Disappearance was also appreciable in the pond and treated county water, both of which were very hard; 45% of the hydrazine disappeared within the first hour and 90-97% disappeared after 1 day. The stored laboratory water, which contained no organic matter and was less hard than the river and treated county water, did not degrade hydrazine significantly until the second day and only ~35% by the fourth day. Treated city water contained near the original amount of hydrazine after 4 days. Additional experiments indicated that the variability in the rates of hydrazine disappearance in

the above water was not due to differences in temperature or dissolved oxygen levels, but partly to hardness; the concentration of hydrazine (5 ppm) in soft water (24 ppm $CaCO_3$) remained unchanged except for a small (8%) decrease at 96 hours, whereas it was reduced 21% in water of 110 ppm hardness and ~50% in moderately hard (216 ppm) to hard (420 ppm) water after 72-96 hours. Although hardness apparently contributed to hydrazine degradation, it was speculated that organic matter was a primary contributor to the degradation.

MacNaughton et al. (1981) briefly summarized the results of experiments in which the degradation of 3.2 ppm hydrazine was monitored in distilled, pond and seawater over a period of 6 days. The pH was 8.0 and the temperature was 25°C, but additional detail regarding the design of the study was not provided. Loss of hydrazine from the distilled water was too low to be measured, but ~20 and 40% loss occurred in the pond and sea-water, respectively. The hydrazine loss (presumed to be due to oxidation) reportedly could not be correlated with chloride content, ionic strength or suspended material, and was speculated to be due to low concentrations of metals (e.g., copper) that could have acted as catalysts.

The biodegradation of hydrazine sulfate by four cultures of microorganisms ubiquitous in aquatic environments was studied by Kane and Williamson (1983). These included two cultures of nitrifying bacteria (Nitrosomonas and Nitrobacter), an unspecified culture of denitrifying bacteria and an unspecified culture of anaerobic bacteria. When tested with Nitrobacter, Nitrosomonas or the denitrifiers at a concentration of 50 ppm without added nutrients, it was found that hydrazine degraded ~20% in 7 days; with typical nutrients added (NH_4^+, NO_2^-, NO_3^-, PO_4^{-3}, HCO_3^-), the aerobic degradation after 7 days was ~50%. The loss of

hydrazine during a 6-day bioassay with the anaerobic bacteria was ~25% (nutrient status not reported). Toxic concentrations of hydrazine, defined as the concentration required to reduce substrate metabolism by 50%, were estimated in dose-response studies to be 14.6, 1.4, 4.3 and 36 ppm for the Nitrobacter, Nitrosomonas, denitrifying and anaerobic bacteria, respectively. Additional experiments in which Nitrosomonas was cultured with 71.5-146 mg/ℓ ^{15}N-hydrazine sulfate for 3-9 hours showed that the primary degradation product was nitrogen gas (average hydrazine-N recovery of 65%), and not NH_4^+, NO_2^- or NO_3^-. The slow degradation and high toxicity of hydrazine, even at low concentrations, indicate that biodegradation may not be a significant removal process in aquatic media.

Petri plates (9.0 cm diameter) that were filled with 25% aqueous hydrazine were maintained under conditions of controlled air velocity (63.5 cm/sec at the evaporating surface) and temperature (21±1°C) (Stauffer, 1977; MacNaughton et al., 1981). Approximately 8% of the mass was lost due to evaporation in the first 6 hours and ~21% in the following 4.8 days. Other experiments indicated that initial evaporation of hydrazine increased at higher concentrations, and that evaporation increased in the presence of sunshine (due to thermal rather than photochemical effects). The measured evaporation rate of hydrazine from petri plates under the above conditions was 0.49 mg/cm² min, but concentration was not stated. Evaporation of hydrazine may be minimal at ppm concentrations due to its miscibility, but data at low concentrations are not available. The relevance of the above evaporation data to actual environmental conditions is unclear, since the simulation did not adequately represent other parameters such as water depth.

2.3. SOIL

The absorption and leaching characteristics of hydrazine in pure sand, organic soil (1% carbon, 1% clay, 96% sand), sand with a trace of clay (99%

sand, 0.4% clay) and a 1:9 mixture of sand and clay (69% sand, 28% clay) were studied by Braun and Zirrolli (1983). In pure sand, negligible adsorption of hydrazine was observed (1%) and ~89% of the compound could be leached with water from a 20 cm column (10 mL of a 0.1% v/v solution of hydrazine was applied). In the three other soils, adsorption varied from 53-77%; of these total amounts of adsorbed hydrazine, 14-28% could not be recovered by elution with 0.1 N HCl, presumably due to reactive processes in the soil. The leaching of hydrazine with water from the three soils varied from 1.3-1.6% (organic and trace clay soils) to 7.6% (1:9 clay-sand mixture). These data indicate that leaching of hydrazine will be slowest in soils with a high cation exchange capacity, particularly in soils with a high clay content.

The above data indicate that hydrazine may undergo substantial reactions in soils, and that some leaching from soil to groundwater is possible. Although it is indicated that leaching of hydrazine will be slowest in soils with a high cation exchange capacity, particularly in soils with a high clay content, the correlation between adsorption/degradation and leaching and particular soil characteristics has not been firmly established.

3. EXPOSURE

Hydrazine has been monitored at a concentration of 0.01 mg/ℓ in an outflow pipe from an industrial facility in Lackawanna, NY (STORET). Additional monitoring data for hydrazine in water, or monitoring data for hydrazine in air or food were not located in the available literature. The high reactivity of hydrazine indicates that hydrazine will degrade rapidly via chemical pathways (e.g., reaction with oxidants) in the environment, and that ambient exposure will probably be negligible. The potential for human exposure does exist, however, during the manufacture, transportation and use of this chemical.

4. PHARMACOKINETICS

4.1. ABSORPTION

Pertinent data regarding the gastrointestinal or respiratory absorption of hydrazine were not located in the available literature. Dermal absorption in dogs occurs, since hydrazine was detected in the blood within 30 seconds of application of 5-15 mmol/kg (~160-480 mg/kg) to shaved skin (Smith and Clark, 1972). Within 20 minutes of application of 15 mmol/kg, the mean plasma level of hydrazine in four dogs was 35 µg/mL. The plasma levels continue to rise to 55 µg/mL at 60 minutes, after which the level remained constant for an additional 300 minutes.

4.2. DISTRIBUTION

Tissue distribution studies have been conducted with single subcutaneous injections of 60 mg/kg hydrazine in Sprague-Dawley rats (Dambrauskas and Cornish, 1964) and single i.p. injections of 32 mg/kg hydrazine sulfate in Swiss-Webster mice (Nelson and Gordon, 1982). When sacrificed 2 hours after injection, the kidneys had the highest concentrations of hydrazine; the kidney concentrations were ~3-fold higher than the lungs, heart, brain and visceral tissues, which had comparable levels. Fat was analyzed in the rat study and showed hydrazine levels that were ~10 times lower than the non-kidney tissues. It appears that hydrazine was not retained selectively in the lungs (the primary target organ for tumorigenicity) or any of the tissues, as distribution was qualitatively the same (although concentrations were much lower) 20-24 hours after injection.

4.3. METABOLISM

Few studies have been conducted on the metabolism of hydrazine due to the lack of an appropriate radioisotope of nitrogen and a lack of specific and sensitive assays for hydrazine.

Recent studies with rodents, which utilized ^{15}N-labeled hydrazine and mass spectrametric analyses, have shown that significant portions of single 32 mg/kg i.p. doses are expired as $^{15}N_2$ gas. Approximately 25% of the dose in rats was expired as N_2 within 48 hours, but most (~15%) appeared within 30 minutes of administration (Springer et al., 1981). In the mice, N_2 expiration accounted for ~20% of the dose within the first 1-2 hours and 30-35% after 48 hours (Nelson and Gordon, 1982). The evolution of N_2 was much slower and relatively constant with time after the initial rapid phase, and appeared to correlate with the biphasic disappearance of hydrazine from the blood in both species. In vitro studies with mice indicated that much of the oxidation occurred in the blood in the presence of oxyhemoglobin, although liver microsomal oxygenases were also capable of oxidizing hydrazine to nitrogen (Nelson and Gordon, 1982).

Approximately 30% of the administered 32 mg/kg i.p. dose in rats and 15% in mice was excreted in the urine as hydrazine within 48 hours, with an additional 20 and 25% of the dose, respectively, excreted as an unidentified derivative(s) that is acid-hydrolyzable to hydrazine (Springer et al., 1981; Nelson and Gordon, 1982). An acid-hydrolyzable derivative(s) of hydrazine was also found in the blood of the rats (Springer et al., 1981).

Although the identity of the acid-hydrolyzable derivative(s) was not established in the above studies, Springer et al. (1981) noted that "very small" amounts of mono-and diacetylhydrazine were present. Other studies also suggested that acetylation may be a metabolic pathway for hydrazine. McKennis et al. (1955) administered a single 24 mg/kg dose of hydrazine to 15 rabbits by i.p. injection and recovered an average of 12.5% of the hydrazino nitrogen in the urine; 2.3% of the hydrazino nitrogen was identified as 1,2-diacetylhydrazine and the rest (10.2%) was unchanged hydrazine.

The duration of this study, however, was not specified. Wright and Timbrell (1978) found 13.7% of administered hydrazine hydrate in the urine of rats 24 hours after i.p. injection of 5.1 mg/kg; small amounts of mono- and diacetylhydrazine were identified (2.2 and 1.2% of the dose, respectively), but almost all (10.3%) was hydrazine.

Intravenous administration of 16 mg/kg hydrazine (single dose) to 2 dogs produced unchanged hydrazine in the urine (4.3 and 6.6% of the dose in an unspecified amount of time), but no 1,2-diacetylhydrazine (McKennis et al., 1959). One dog that was intravenously injected with 15 mg/kg hydrazine sulfate excreted 13% of the dose in 45 hours entirely as unchanged hydrazine (McKennis et al., 1959).

^{15}N-ammonia was not detected in the urine of rats that were given single i.p. injections of 32 mg/kg ^{15}N-hydrazine (Springer et al., 1981).

4.4. EXCRETION

Hydrazine and its metabolites appear to be eliminated primarily via the urine and respiratory tract. Metabolism studies with rats and mice (summarized in Section 4.3.) accounted for ~70-75% of a single 32 mg/kg i.p. dose of hydrazine by these routes within 48 hours (Springer et al., 1981; Nelson and Gordon, 1982).

In Swiss-Webster mice, 30-45% of single i.p. doses of 32 mg/kg hydrazine was excreted in the urine within 48 hours as hydrazine (10-15%) and acid-hydrolyzable derivatives (20-25%) (Nelson and Gordon, 1982). Approximately 50% of 40 and 60 mg/kg subcutanoues doses of hydrazine was excreted unchanged in the urine of Swiss ICR mice within 48 hours (Dambrauskas and Cornish, 1964). Springer et al. (1981) found that ~52% of a 32 mg/kg i.p. dose of hydrazine was excreted in the urine of Sprague-Dawley rats by 48 hours, with ~29 and 21% as hydrazine and acid-hydrolyzable derivatives,

respectively. Approximately 27% of a 60 mg/kg subcutaneous dose was excreted in the urine of Sprague-Dawley rats 20 hours after injection (Dambrauskas and Cornish, 1964). Wright and Timbrell (1978), however, found only 13.7% of hydrazine in the urine 24 hours after i.p. injection of 5 mg/kg hydrazine hydrate to rats.

Approximately 25% and 30-35% of a single 32 mg/kg i.p. dose of hydrazine was expired as N_2 gas in rats (Springer et al., 1981) and mice (Nelson and Gordon, 1982), respectively, within 48 hours.

Springer et al. (1981) noted that rats given single i.p. doses of 32 mg/kg hydrazine eliminated no more than 1% of the dose in the bile. It was not determined, however, if metabolites not measurable as hydrazine or hydrolyzable derivatives were present in the bile.

5. EFFECTS

5.1. CARCINOGENICITY

Interest in the carcinogenic activity of hydrazine and hydrazine sulfate has been primarily related to the fact that hydrazine is the principal metabolite of isonicotinic acid hydrazide (isoniazid), an antituberculous drug. More recently, the toxicology of hydrazine has been the subject of research by the U.S. Air Force because of its use as a propellant.

Numerous studies have demonstrated that orally administered hydrazine, usually given as hydrazine sulfate, induces high incidences of pulmonary tumors in different strains of mice (IARC, 1973; Biancifiori, 1969, 1970a,b,c, 1971; Biancifiori and Severi, 1966; Biancifiori and Ribacchi, 1962a,b; Biancifiori et al., 1963a,b, 1964; Milia, 1965; Roe et al., 1967; Toth, 1969, 1971; Kelly et al., 1969; Yamamoto and Weisburger, 1970; Bhide et al., 1976). The tumors were often multiple and were generally characterized as adenomas and adenocarcinomas. Hepatomas and hepatocarcinomas were also observed in three strains of mice that were treated orally with hydrazine sulfate and also developed lung tumors (IARC, 1973); these include BALB/c/Cb/Se mice (Biancifiori, 1970a,b), CBA/Cb/Se mice (Biancifiori, 1970d; Biancifiori et al., 1964; Severi and Biancifiori, 1967, 1968) and C3Hb/Cb/Se mice (Biancifiori, 1971). The experimental design and results of representative studies are summarized in Table 5-1, and those most relevant to quantitative risk assessment are discussed below. It appears from the IARC (1973) review and the available English papers that only some of the mouse studies employed multiple dose levels (Biancifiori, 1970a,d; Milia, 1965), lifetime administration, or administration in the drinking water (Toth, 1969, 1972).

TABLE 5-1

Carcinogenicity of Hydrazine

Compound	Route (Vehicle)	Species/ Strain	Sex	Dose	Treatment Duration	Study Duration	Tumor Type	Tumor Incidence	Reference
Hydrazine	drinking (water)	mouse/Swiss	M	0.001% (0.069 mg/day)	life (104 wk)	life (104 wk)	lung adenoma or carcinoma	24/50	Toth, 1972a
							lung adenoma	15/50	
				0%	NA	life (104 wk)	lung adenoma or carcinoma	10/110[a]	
							lung adenoma	10/110[a]	
			F	0.001% (0.056 mg/day)	life (104 wk)	life (104 wk)	lung adenoma or carcinoma	27/50	
							lung adenoma	18/50	
				0%	NA	life (114 wk)	lung adenoma or carcinoma	14/110[a]	
							lung adenoma	12/110[a]	
Hydrazine	gavage (water)	mouse/Swiss	F	0.25 mg/day, 5 days/wk	40 wk	50-60 wk	lung tumors	4/4	Roe et al., 1967
				0 mg/day	NA	50-60 wk	lung tumors	6/42	
Hydrazine sulfate	drinking (water)	mouse/Swiss	M	0.012% (0.74 mg/day)	life (84 wk)	life (84 wk)	lung adenoma or carcinoma	25/50	Toth, 1969
							lung adenoma	18/50	
				0%	NA	life (104 wk)	lung adenoma or carcinoma	10/110	
							lung adenoma	10/110	
			F	0.012% (0.65 mg/day)	life (84 wk)	life (84 wk)	lung adenoma or carcinoma	24/50	
							lung adenoma	18/50	
				0%	NA	life (114 wk)	lung adenoma or carcinoma	14/110	
							lung adenoma	12/110	
Hydrazine sulfate	gavage (water)	mouse/ CBA/Cb/Se	M	1.13 mg/day	36 wk	89 wk	lung adenoma or carcinoma	16/21	Severi and Biancifiori, 1968
							liver carcinoma	13/21	
				0 mg/day	NA	148 wk	lung adenoma or carcinoma	1/37	
							liver carcinoma	4/37	
			F	1.13 mg/day	36 wk	79 wk	lung adenoma or carcinoma	19/21	
							liver carcinoma	15/21	
				0 mg/day	NA	99 wk	lung adenoma or carcinoma	4/47	
							liver carcinoma	2/47	

TABLE 5-1 (cont.)

Compound	Route (Vehicle)	Species/ Strain	Sex	Dose	Treatment Duration	Study Duration	Tumor Type	Tumor Incidence	Reference
Hydrazine sulfate	gavage (water)	mouse/BALB/c	F (virgin)	1.13 mg/day (170 mg total)	150 days	NR[c]	lung tumors	20/22[d]	Biancifiori, 1970b
				0 mg/day	NA	NR[c]	lung tumors	1/25	
			F (breeder)	1.13 mg/day (170 mg total)	150 days	NR[c]	lung tumors	25/25[d]	
					150 days	NR[c]	liver carcinoma	7/25	
					150 days	NR[c]	ovarian tumors	6/25[e]	
				0 mg/day	NA	NR[c]	lung tumors	2/25	
					NA	NR[c]	liver carcinoma	0/25	
					NA	NR[c]	ovarian tumors	0/25	
			F (gonadec-tomized)	1.13 mg/day (170 mg total)	150 days	NR[c]	lung tumors	15/25[d]	
				0 mg/day	NA	NR[c]	lung tumors	7/26	
Hydrazine sulfate	gavage (water)	mouse, CBA/Cb/Se	M	1.13 mg/day, 6 days/wk	25 wk	87 wk	liver carcinoma	15/25	Biancifiori, 1970d[f]
				0.56 mg/day, 6 days/wk	25 wk	78 wk	liver carcinoma	12/25	
				0.28 mg/day, 6 days/wk	25 wk	76 wk	liver carcinoma	7/25	
				0.14 mg/day, 6 days/wk	25 wk	98 wk	liver carcinoma	1/26	
				0 mg/day	NA	100 wk	liver carcinoma	3/30	
			F	1.13 mg/day, 6 days/wk	25 wk	87 wk	liver carcinoma	15/24	
				0.56 mg/day, 6 days/wk	25 wk	78 wk	liver carcinoma	16/24	
				0.28 mg/day, 6 days/wk	25 wk	76 wk	liver carcinoma	2/25	
				0.14 mg/day, 6 days/wk	25 wk	98 wk	liver carcinoma	0/25	
				0 mg/day	NA	100 wk	liver carcinoma	1/29	
Hydrazine sulfate	gavage (water)	rat/Cb/Se	M	18 mg/day	68 wk	109 wk	lung adenoma or carcinoma	3/14	Severi and Biancifiori, 1968
							liver tumors[g]	4/13	
				0 mg/day	NA	109 wk	lung adenoma or carcinoma	0/28	
							liver tumors[g]	0/28	

TABLE 5-1 (cont.)

Compound	Route (Vehicle)	Species/ Strain	Sex	Dose	Treatment Duration	Study Duration	Tumor Type	Tumor Incidence	Reference
			F	12 mg/day	68 wk	109 wk	lung adenoma or carcinoma	5/18	
				0 mg/day	NA	109 wk	lung adenoma or carcinoma	0/22	
Hydrazine	Inhalation	rat/F344	M	5.0 ppm (6.6 mg/m³), 6 hr/day, 5 days/wk	52 wk	130 wk Animals were sacrificed 18 monthes post-exposure and 17 months exposure	nasal cavity epithelial		MacEwen and Vernot, 1980
							benign	66/99	
							malignant	6/99	
							thyroid adeno-carcinoma	13/99	
				1.0 ppm (1.3 mg/m³), 6 hr/day, 5 days/wk	52 wk	130 wk	nasal cavity epithelial		
							benign	10/98	
							malignant	1/98	
							thyroid adeno-carcinoma	13/99	
				0.25 ppm, (0.32 mg/m³) 6 hr/day, 5 days/wk	52 wk	130 wk	nasal cavity epithelial		
							benign	2/99	
							malignant	0/99	
							thyroid adeno-carcinoma	7/99	
				0.05 ppm, (0.51 mg/m³) 6 hr/day, 5 days/wk	52 wk	130 wk	nasal cavity epithelial		
							benign	2/99	
							malignant	1/99	
							thyroid adeno-carcinoma	5/99	
				0 ppm	NA	130 wk	nasal cavity epithelial		
							benign	0/149	
							malignant	0/149	
							thyroid adeno-carcinoma	7/149	
			F	5.0 ppm, (6.6 mg/m³) 6 hr/day, 5 days/wk	52 wk	130 wk	nasal cavity epithelial		
							benign	31/98	
							malignant	5/98	
				1.0 ppm, (1.3 mg/m³) 6 hr/day, 5 days/wk	52 wk	130 wk	nasal cavity epithelial		
							benign	4/97	
							malignant	0/97	

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Compound	Route (Vehicle)	Species/ Strain	Sex	Dose	Treatment Duration	Study Duration	Tumor Type	Tumor Incidence	Reference
				0.25 ppm (0.32 mg/m³), 6 hr/day, 5 days/wk	52 wk	130 wk	nasal cavity epithelial		
							benign	0/100	
							malignant	0/100	
				0.05 ppm (0.07 mg/m³), 6 hr/day, 5 days/wk	52 wk	130 wk	nasal cavity epithelial		
							benign	1/99	
							malignant	0/99	
				0 ppm	NA	130 wk	nasal cavity epithelial		
							benign	0/147	
							malignant	0/147	
Hydrazine	Inhalation	mouse/C57B1/6	F	1.0 ppm (1.3 mg/m³), 6 hr/day	52 wk	78 wk	lung adenoma	12/379	MacEwen and Vernot, 1980
				0 ppm	NA		lung adenoma	4/378	
				0.25 ppm (0.32 mg/m³), 6 hr/day, 5 days/wk	52 wk	78 wk	lung adenoma	5/382	
				0.05 ppm (0.07 mg/m³), 6 hr/day, 5 days/wk			lung adenoma	3/364	
				0 ppm	NA	78 wk	lung adenoma	8/385	

[a]Control data from Toth, 1969

[b]Tumor-bearing animals/survivors at 50-60 weeks

[c]Mice sacrificed when moribund

[d]The percentages of pulmonary tumors that were classified as adenomas and carcinomas in the virgin, breeder and gonadectomized mice were 96.6 and 3.3%, 52.7 and 47.2%, and 96.0 and 4.0%, respectively.

[e]Includes 4 mice with luteomas and 2 with granulosa cell tumors

[f]Pulmonary tumors present in "many" treated mice but not quantified

[g]Carcinomas or spindle cell sarcomas

NA = Not applicable; NR = Not reported

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Toth (1969) administered 0.012% hydrazine sulfate in the drinking water of groups of 40-50, 6-week-old Swiss, C3H and AKR mice of each sex for life. Groups of 110 Swiss mice and 30 C3H and AKR mice of each sex served as untreated controls. The mice were either allowed to die or were sacrificed when moribund, and histologic examinations of the liver, spleen, kidney, at least four lobes of the lungs and other organs that showed gross pathologic changes were conducted on all animals. As detailed in Table 5-1, continuous lifetime treatment with 0.012% hydrazine sulfate in the drinking water produced pulmonary adenomas and adenocarcinomas in 46-50% of the treated Swiss mice, compared with 9-11% in the controls. The average daily hydrazine sulfate consumption per Swiss mouse was reported to be 0.74 mg for the males and 0.65 for the females. Hydrazine sulfate treatment did not induce a significantly increased incidence of tumors at other sites in the Swiss mice or at any site in the C3H or AKR mice, but it was noted that the treatment did substantially decrease the incidence of mammary gland adenocarcinomas in the C3H females.

Similar results were obtained in a similarly designed study in which 0.001% hydrazine in the drinking water was administered continuously for the lifespan of 50 male and 50 female Swiss mice, which were 6 weeks old at the beginning of treatment (Toth, 1972a). The average daily consumption of hydrazine per mouse was 0.069 mg for males and 0.056 mg for females. The hydrazine treatment reportedly induced pulmonary adenomas and adenocarcinomas in 48-54% of the mice, but elevated incidences of tumors at other sites were not reported. Concurrent controls were not, however, used in this study; the incidences of tumors in untreated control Swiss mice from the earlier Toth (1969) study served as a reference.

Biancifiori (1970b) conducted a multiple dose study in which hydrazine sulfate was administered by gavage to groups of 24-30, 8-week-old CBA/Cb/Se mice of each sex at doses of 0, 0.14, 0.28, 0.56 or 1.13 mg/day, 6 days/week for 25 weeks. If it is assumed that the mice weighed 0.03 kg, the corresponding doses would be 0, 4.7, 9.3, 18.7 or 37.7 mg/kg. Histological examination of the livers, lungs, unspecified endocrine glands and other tissues that were suspected of having lesions were conducted on all mice when moribund or at the time of natural death. Multiple pulmonary tumors were reportedly present in "many" of the treated mice, but incidences were not reported because the purpose of this study was to describe hepatic tumors. Hepatic tumors, classified as very vascularized hepatocarcinomas, were induced in a dose-related manner in both sexes (see Table 5-1); lung metastases were observed in some of the high-dose (37.7 mg/kg) mice. A multiple dose study that was not available for independent review showed that similar gavage administration of hydrazine sulfate also resulted in dose dependent induction of pulmonary tumors in the same strain of mice (Biancifiori, 1970a).

Milia (1965) treated 25 newborn BALB/c/Cb/Se mice with increasing doses of hydrazine sulfate that ranged from 25-600 µg/day by gavage for 60 days (IARC, 1973). A total dose of 17 mg had been administered when the mice were sacrificed at 18 weeks of age; 96% had lung tumors, with an average of three tumors/mouse.

One available study evaluated the oral carcinogenicity of hydrazine sulfate in rats. Severi and Biancifiori (1968) administered daily doses of hydrazine at 18 mg/day to 14 male and 12 mg/day to 18 female Cb/Se rats by gavage from the age of 8 weeks for 68 weeks. Untreated groups of 28 male and 22 female rats were used as controls, and the liver, lungs and other

organs that showed macroscopic lesions were examined histologically at the time of natural death. Lung tumors (adenomas or adenocarcinomas) were found in 3 of the 14 males and in 5 of the 18 females after 109 weeks, but in none of the untreated controls. Liver tumors (hepatic cell carcinomas or spindle cell carcinomas) occurred in 4 of 13 treated male rats, but in none of 13 treated females nor in any of the untreated controls. It was noted that spontaneous liver tumors had never been observed in Cb rats maintained in the same laboratory during the previous 14 years.

Administration of hydrazine sulfate to Syrian golden hamsters in the drinking water at a concentration of 0.012% (average dose 2.3 mg/day) for life (Toth, 1972b) or by gavage at doses of 2.8 mg/day (10 applications in 20 weeks) or 3.0 mg/day (60 applications in 15 weeks) (Biancifiori, 1970b) did not produce significant increases in the incidence of tumors after lifetime observation.

The results of an Air Force Aerospace Medical Research Laboratory-sponsored chronic inhalation study, in which groups of 100 F344 rats of each sex, 400 female C57Bl/6 mice and 4 beagle dogs of each sex were exposed to 0.25 or 1.0 ppm hydrazine 6 hours/day, 5 days/week for 1 year, were summarized by MacEwen and Vernot (1980). Groups of 100 rats of each sex and 400 female mice were also similarly exposed to 0.05 ppm hydrazine, and 100 rats of each sex were similarly exposed to 5.0 ppm hydrazine. Chamber controls consisted of groups of 150 rats of each sex, 800 female mice and 8 dogs of each sex. Surviving rats and mice were sacrificed 18 months postexposure and surviving dogs were sacrificed 38 months postexposure for comprehensive histological examination. As detailed in Table 5-1, significantly increased incidences of tumors were found at the highest exposures in the male rats (nasal cavity epithelial and pituitary adenocarcinoma), female rats (nasal

cavity epithelial) and female mice (lung adenomas). Treatment-related neoplasms were not observed in the dogs.

5.2. MUTAGENICITY

Hydrazine mutagenicity has been demonstrated in numerous assays, including many validation studies. Because hydrazine is carcinogenic, only a brief overview of mutagenicity will be presented. This overview is based on a review by Kimball (1977) and on representative studies that appeared subsequently and were available for review. Hydrazine is a direct-acting mutagen and was often tested as hydrazine sulfate, hydrazine hydrate or hydrazine hydrochloride.

In vitro studies have shown that hydrazine can cleave both thymine and cytosine rings (leading to a loss of pyrimidines), saturate the 5,6 double bond of pyrimidines, and form N^4-aminocytosine (Kimball, 1977). Intraperitoneal treatment of mice with hydrazine sulfate (64 mg/kg) and radiolabeled formate or methionine, as sources of C_1 units, produced radiolabeled 7-methylguanine in liver DNA and RNA, indicating hydrazine mediated indirect alkylation of nucleic acids in vivo (Quintero-Ruiz et al., 1981). Hydrazine-induced DNA strand breaks have been demonstrated, as measured by alkaline elution techniques, in rat hepatocytes treated in vitro (Sina et al., 1983) and in the liver and lung of mice that were treated intraperitoneally with 156 mg/kg hydrazine hydrate (Parodi et al., 1981). Testicular DNA synthesis was inhibited in mice by single oral doses of 200 mg/kg hydrazine (Seiler, 1977); however, unscheduled DNA synthesis was not induced in human fibroblasts treated with hydrazine in vitro (Whiting et al., 1979) or in sperm cells of mice treated with 10-120 mg/kg hydrazine by i.p. injection (Sotomayor et al., 1982). DNA damage was also indicated by differential growth inhibition of DNA repair-deficient and repair-proficient strains of

Escherichia coli and Bacillus subtilis (Von Wright and Tikkanen, 1980; Suter and Jaeger, 1982).

Reverse mutations were induced by hydrazine in histidine auxotrophs of Salmonella typhimurium when the bacteria were treated in vitro (Kimball, 1977; Anderson and Styles, 1978; McMahon et al., 1979; Tosk et al., 1979; Parodi et al., 1981; Rogan et al., 1982) and in a host-mediated assay with mice that were given a single dose of 420 mg/kg hydrazine sulfate by gavage (Simmon et al., 1979). In vitro treatment with hydrazine also induced reverse mutations in tryptophan auxotrophs of Escherichia coli (McMahon et al., 1979; Von Wright and Tikkanen, 1980). Mitotic recombination, however, was not increased in Saccharomyces cerevisiae D3 that were treated with hydrazine sulfate in vitro (Simmon, 1979) or in a host-mediated assay with mice treated intraperitoneally with 420 mg/kg (Simmon et al., 1979).

Conflicting reports of mutation to thymidine resistance in cultured L5178Y mouse lymphoma cells are available (Rogers and Back, 1981; Amacher et al., 1980), but mutation to ouabain, thioguanine or cytosine arabinoside resistance was not reported (Rogers and Back, 1981). Sister-chromatid exchanges were induced by in vitro treatment with hydrazine in Chinese hamster V-79 cells (Speit et al., 1980), Chinese hamster ovary cells (MacRae and Stich, 1979) and Chinese hamster Don (lung) cells (Baker et al., 1983), but micronuclei were not produced in mouse colonic cells treated in vitro (Heddle et al., 1982).

Hydrazine has been reported to induce a variety of morphological, physiological and color mutants in crop plants (e.g., barley, maize, rice, tomato) when the seeds were soaked in hydrazine (Kimball, 1977). Hydrazine also induced both specific-locus and recessive-lethal mutations in Drosophila melanogaster (Jain and Shukla, 1972; Shukla, 1972). Hydrazine did not

induce dominant lethal mutations in mice (Epstein and Shafner, 1968; Epstein et al., 1972).

5.3. TERATOGENICITY

Lee and Aleyassine (1970) injected hydrazine subcutaneously into 12 pregnant Wistar rats at a dose of 8 mg/kg/day on days 11-21 of gestation. A group of 15 pregnant rats served as vehicle (saline) controls. Maternal deaths occurred in 2 of the treated and none of the control rats, but additional indices of maternal toxicity were not evaluated. Fetotoxicity in the treated group was indicated by a reduced ratio of fetal survivors to implantation sites (37% in treated vs. 79% in controls) and significantly ($p<0.001$) reduced fetal weight. Gross malformations were not observed in the fetuses of the hydrazine-treated rats, but generalized edema and, occasionally, petechial hemorrhages were present. Neonatal survival was determined in additional groups of 12 treated and 15 control rats; none of the hydrazine-treated rats gave birth to newborns that survived the first 24 hours, but newborns from 12 of the control rats survived.

The results of embryotoxicity/teratogenicity studies conducted by the Air Force Aerospace Medical Research Laboratory are available in abstract form (Lyng et al., 1980; Keller et al., 1982). In a study with F344 rats (Keller et al., 1982), hydrazine was intraperitoneally injected at unspecified doses up to 10 mg/kg on days 6-15 of gestation. Dose-related embryolethality and maternal toxicity (not elaborated) were observed at the two highest doses. Injection of 10 mg/kg hydrazine on gestation days 7-9, 10-12 or 13-15 indicated that the most susceptible prenatal period was days 7-9; embryolethality and an increased incidence of anomalies (not elaborated), but not major malformations, were observed in this group. An increase in perinatal mortality was also noted in the offspring of rats injected with 10

mg/kg hydrazine on gestation days 7-9, but neonatal developmental parameters (i.e., weight gain, ear detachment, incisor eruption, eye opening, surface righting, cliff avoidance, forward motion or swimming ability) were not adversely affected. Percutaneous treatment with 50 mg/kg hydrazine on day 9 of gestation reportedly produced a high incidence of embryolethality in F344 rats, but similar treatment with 5 mg/kg was not embryolethal; additional data regarding this experiment were not reported in the abstract.

Intraperitoneal injection of hydrazine at doses of 4, 12 or 20 mg/kg/day on days 6-9 of gestation reportedly had no significant effect on the number of implantations per female, mean number of viable fetuses per litter or mean number of resorptions per litter in ICR mice, but similar treatment with 30 or 40 mg/kg hydrazine was fetotoxic (Lyng et al., 1980). Maternal toxicity was indicated at doses >4 mg/kg by reduced weight gain during the injection period (12 and 20 mg/kg) and mortality (4 of 21 died at 40 mg/kg). Fetal soft-tissue (e.g., exencephaly and hydronephrosis) and/or skeletal (e.g., supernumerary ribs) anomalies reportedly occurred in all groups treated with <40 mg/kg. Additional data regarding this study were not reported in the abstract.

Schiller et al. (1979) examined the effect of a single 260 mg/kg gavage dose of hydrazine hydrate on day 12 of gestation on the development of intestinal brush boarder enzymes in Syrian golden hamsters. It was found that exposure to hydrazine significantly ($p<0.05$) reduced neonatal (3- to 4-day-old) lactase activity, increased neonatal and postnatal (24- to 25-day-old) alkaline phosphatase activity, and elevated postnatal but decreased young adult (53- to 60-day-old) sucrose activity. The number of offspring assayed was not specified, but it was reported that the treatment and control groups comprised 24 mated hamsters each. Head examinations of the

treated neonates revealed normal palate development, but these data were not reported quantitatively.

Additionally, teratogenicity studies of hydrazine that employed natural routes of exposure (oral or inhalation) were not located in the available literature.

5.4. OTHER REPRODUCTIVE EFFECTS

Pertinent data regarding other reproductive effects were not located in the available literature.

5.5. CHRONIC TOXICITY

Administration of hydrazine sulfate to Syrian golden hamsters in the drinking water at concentrations of 0.017-0.026%, 0.034-0.053% or 0.051-0.083% for 9 weeks (23, 46 or 69 mg/kg/day, respectively) produced depressed growth rates and accumulation of methylguanines (7-methylguanine and O^6-methylguanine) in the liver (Bosan and Shank, 1983). The methylation was first detected after 2 days of exposure (groups of four hamsters per dose were sacrificed on days 2, 4, 6, 8, 10, 28 and 63). Histological examinations were not conducted in this study.

Nonneoplastic effects of chronic inhalation exposure to hydrazine were briefly described by MacEwen and Vernot (1980). In this study group of 100 rats of both sexes, 400 female mice or 4 beagle dogs of both sexes were exposed to 0.05-5.0 ppm hydrazine for 1 year (see Section 5.1.). Inflammatory changes of the respiratory tract (e.g., squamous metaplasia of the nasal cavity, larynx and trachea, epithelial hyperplasia of the nasal epithelium and lung, inflammation of the larynx and trachea), were prominent in the rats exposed to 5.0 ppm hydrazine. Respiratory effects were observed in rats that died during exposure as well as those at the 2.5-year terminal sacrifice, and were noted at exposure levels as low as 0.05 ppm in the male

rats (laryngeal/tracheal inflammation and nasal/lung hyperplasia) and 1.0 ppm in the female rats (tracheal inflammation). Signficantly increased ($p<0.05$) incidences of other nonneoplastic lesions were described in the treated rats and included lymph node hyperplasia, glomerulonephrosis, endometrial hyperplasia and endometritis, ovary atrophy and oviduct salpingitis in the 5.0 ppm females, and myocardial degeneration in the 1.0 and 5.0 males. Treatment-related nonneoplastic lesions were not described in the mice or dogs at any of the treatment levels, and it was noted that measurement of bromsulfalein (BSP) retention time during exposure did not indicate impaired liver function in the dogs.

Groups of 50 male Sprague-Dawley rats, 40 female ICR mice, 8 male beagle dogs and 4 female rhesus monkeys were exposed via inhalation intermittently (6 hours/day, 5 days/week) to 1.0 or 5.0 ppm hydrazine and continuously to 0.2 or 1.0 ppm hydrazine for 6 months (Haun and Kinkead, 1973). Unexposed control groups of the same size were used, and toxicity parameters that were evaluated included body weight (rats, monkeys, dogs), clinical chemistry (5 rats/group, dogs, 4 monkeys/group), hematology (dogs and 4 monkeys/group), organ weights (rats, monkeys and dogs) and histology (all animals). Significant mortality occurred only in the mice, was dose-related, and occurred in most instances during the first 2-2.5 weeks of exposure; total mortality in the 0 ppm, 0.2 ppm continuous, 1.0 ppm intermittent, 5.0 ppm intermittent and 1.0 ppm continuous exposure groups was 0, 2.5, 7.5, 35 and 55%, respectively. The mice were not weighed, but rats exhibited a dose-related growth rate depression and dogs showed weight loss at the two highest exposure levels (1.0 ppm continuous and 5.0 ppm intermittent). The rat and monkey clinical chemistry/hematology measurements were normal, but dogs exposed at

the two highest levels had depressed red blood cell counts, decreased hemoglobin values and hematocrits, and increased erythrocyte fragility. The results of the pathological examinations showed that the mortality in the mice was probably due to hepatotoxicity; fatty liver change was a consistent finding in the mice at all exposure levels, and slight to moderate fat accumulation was noted in the exposed monkeys. Treatment-related gross or histopathologic effects were not described in the other species at the end of exposure, but it was noted that high-dose mice (1.0 ppm continuous and 5.0 ppm intermittent) that were alive 1 year postexposure (6-9/group) developed alveolar carcinomas.

Comstock et al. (1954) exposed 30 male Wistar rats, 20 female mice (strain not specified), 10 guinea pigs (strain and sex not specified) and 4 male Beagle dogs to 18 mg/m^3 hydrazine vapor (~13.7 ppm) 6 hours/day, 5 days/week for up to 6 months. By the end of the treatment period, 23 rats, 15 mice, 8 guinea pigs and 2 dogs had died. Necropsies (not characterized) were conducted on the surviving mice and dogs, but not on the other animals; the mice reportedly showed no abnormalities, but the surviving dogs exhibited histological fatty changes in the liver and spleen.

6. AQUATIC TOXICITY

6.1. ACUTE EFFECTS

The acute lethal effects of hydrazine and hydrazine sulfate on freshwater fish have been studied most extensively by research units of the U.S. Air Force. A summary of the available data is presented in Table 6-1. Slonim (1977) reported LC_{50}s for hydrazine in goldfish, Lebistes reticulatus, during static testing in hard and soft water conditions. It was apparent that soft water conditions resulted in higher hydrazine toxicity, with 96-hour LC_{50} values of 3.85 and 0.61 for hard and soft water, respectively. Mean times of survival in hydrazine-contaminated water were 3.8 hours at 6.6 mg/ℓ in soft water and 4.5 hours at 20.0 mg/ℓ in hard water, also indicating the higher toxicity in soft water (Slonim, 1977). In the bluegill sunfish, Fisher et al. (1980) reported 96-hour LC_{50} values of 1.08 and 0.43 during static and flow-through testing, respectively. The disparity was, suggestively, due to evaporative loss of hydrazine from static systems, since a continuous supply of fresh hydrazine-contaminated water was available in the flow-through system. Temperature also influenced hydrazine toxicity to bluegills (Hunt et al., 1981). Warmer water was related to increased hydrazine toxicity, possibly due to metabolic rate changes in the fish. The LC_{50} values reported for tests conducted at 21°C were 37.7, 3.8, 1.7 and 1.2 mg hydrazine/ℓ, respectively, for 1-, 6-, 24-and 96-hour exposures. Comparatively, values reported for tests at 10°C were 265, 12.9, 7.7 and 1.6 mg/ℓ, respectively, for the same exposure durations.

Early studies in trout reported that death occurred within 22-25 minutes after exposure at 146 mg hydrazine/ℓ (Corti, 1951). Trout exposed at 0.7 mg/ℓlost equilibrium within 24 hours of exposure (McKee and Wolf, 1963).

TABLE 6-1

Acute Lethal Effects of Hydrazine to Freshwater Fish

Species	Duration	Concentration (mg/ℓ)	Method	Effect	Reference
Goldfish, *Lebistes reticulatus*	24 h	4.60	static[a]	LC_{50}	Slonim, 1977
	48 h	3.98			
	72 h	3.85			
	96 h	3.85			
Goldfish, *L. reticulatus*	24 h	3.32	static[b]	LC_{50}	Slonim, 1977
	48 h	1.58			
	72 h	0.82			
	96 h	0.61			
Goldfish, *L. reticulatus*	28.2 h	2.0[b]	static	LT_{100}	Slonim, 1977
	3.8 h	6.6[b]			
	4.5 h	20.0[a]			
	1.5 h	66.0[a]			
	1.0 h	200.0[a]			
Bluegill sunfish, *Lepomis macrochirus*	96 h	1.08	static	LC_{50}	Fisher et al., 1980
	96 h	0.43	flow-through	LC_0	
Bluegill sunfish, *L. macrochirus*	1	37.7[d]	static	LC_{50}	Hunt et al., 1981
	6	3.8[d]			
	24	1.7[d]			
	96	1.2[d]	flow-through	LC_{50}	
Fingerling Trout (species not specified)	24 h	0.7	NR	loss of equilibrium, death	McKee and Wolf, 1963

TABLE 6-1 (cont.)

Species	Duration	Concentration (mg/ℓ)	Method	Effect	Reference
Trout (species not specified)	22-25 minutes	146	NR	death	Corti, 1951
Larval Lamprey, Petromyzon marinusal	24 h	5.0[c]	NR	no effect	Applegate et al., 1957

[a]Hard water conditions (400-500 mg $CaCO_3$/ℓ)
[b]Soft water conditions (20-25 mg $CaCO_3$/ℓ)
[c]Hydrazine sulfate was the test compound
[d]Values reported are for testing at 21°C. Toxicity was lower at 15.5 or 10.0°C.
NR = Not reported

Applegate et al. (1957) reported that no effects on larval lampreys were evident following 24 hours of exposure at 5.0 mg hydrazine sulfate/ℓ.

E.2. CHRONIC EFFECTS

Mid-cleavage-stage embryos of fathead minnows, Pimephales promelas, were exposed for 48 hours to hydrazine at 0.01, 0.1, 1.0 and 5.0 mg/ℓ in a simulation study of an accidental spill (Henderson et al., 1981). After the 48-hour exposure, embryos were maintained in untreated water until hatching and for 2 weeks post-hatching. Slight effects (loss of eye and body pigment, heartbeat changes and lack of hemoglobin) were noted among embryos exposed at 0.1 mg/ℓ, and these effects and developmental arrest were noted at higher dose levels during the exposure period. Hatching success and hatching time were significantly impeded by exposure to 1.0 and 5.0 mg hydrazine/ℓ. Hatching success was 96% in controls (occurring between 8 and 10 days of age) and 82 (occurring between day 10 and 13) and 2% (occurring on day 12), respectively, in groups exposed at 1.0 and 5.0 mg/ℓ. Abnormalities among larval minnows exposed to 1.0 mg hydrazine/ℓ included scoliosis (100%), pericardial/cardial changes (95%), enlarged abdomen (84%), gaping mouth, decreased hemoglobin (38%) and lack of body movement (26%). A level of 1.0 mg hydrazine/ℓ for acute exposures was regarded as a detrimental level for survival of fathead minnow embryos.

Simulating the accidental spillage of hydrazine, Henderson et al. (1983) exposed embryolarval stages of rainbow trout, Salmo gairdneri, to 0.01, 0.1, 1.0 and 5.0 mg/ℓ on days 12 and 13 of development. Embryos were maintained in a recirculating flow-through system with toxicant-free water until hatching (~26 days of age). Mortality of embryos during the 48-hour treatment period was ~6% in control and treatment groups. Exposed embryos showed a dose-related decrease in skeletal muscle activity and also had abnormal

jaw development. Hatching success (ranging from 99% in controls to 91% in 5.0 mg/.-treated embryos) was not significantly affected in hydrazine-treated groups. Larval length at hatching was significantly decreased in groups treated at 1.0 and 5.0 mg hydrazine/ℓ. Abnormalities occurring among the group exposed to 5.0 mg hydrazine/ℓ and not among controls were scoliosis (53% of treated embryos), downward-curved tail (29%), ruffled fin (32%), bubbled tail (57%) and gaping jaw (73%). When larvae with abnormalities were maintained in toxicant-free water for 5 weeks post-hatching all conditions except severe scoliosis were corrected.

In several publications, Greenhouse (1975, 1976, 1977) reported the effects of hydrazine on embryos and tadpoles of the frog, Xenopus laevis. Embryos were exposed at 0.1, 1.0, 10.0, 25.0, 50.0, 75.0 and 100.0 mg hydrazine/ℓ, and larvae were exposed at 0.01, 0.1, 1.0 and 10.0 mg/ℓ. Embryos were more tolerant of hydrazine than were larval stages. Embryos exposed at 5.0 mg/ℓ developed normally, while larvae exposed at 1.0 mg/ℓ died within 48 hours. A concentration of 0.1 mg/ℓ did not detrimentally affect the development and metamorphosis of X. laevis tadpoles. Abnormalities among embryos and larvae included skeletal deformation, enlarged notochord, trunk shortening and twisting of the tail.

6.3. PLANT EFFECTS

The effects of hydrazine on the unicellular algae, Selenastrum capricornutum, was examined by Scherfig and Dixon (1975). Cultures of the alga, both axenic and bacterized, were exposed to hydrazine at 1.0 and 10.0 µℓ/ℓ (1.0 and 10.0 mg/ℓ). Algal cell growth was 12-14% of controls ($p<0.001$) at both hydrazine levels (in low-nutrient media). Cell number was also significantly ($p<0.001$) decreased to 4-5% of controls. In low-nutrient media, algal cell growth had not recovered by 28 days of treatment, while

cultures exposed at 1 mg/ℓ in high-nutrient media began to recover after ~18 days and were near normal after 28 days.

6.4. RESIDUE

Pertinent data regarding the accumulation and persistence of hydrazine or its residues in aquatic organisms were not located in the available literature.

6.5. OTHER RELEVANT INFORMATION

The behavior and activity of fish were altered following exposure to sublethal levels of hydrazine (Fisher et al., 1980, 1982). Bluegills exposed to 0.1, 0.43, 0.5, 0.73 or 1.0 mg hydrazine/ℓ in static or continuous-flow systems showed aggressive behavior in attacking a food item (prey) (Fisher et al., 1980). Fisher et al. (1982) monitored fish activity by measuring water movements using strain guage detectors. Fish exposed to hydrazine at 1.0 mg/ℓ appeared to have little effect on the swimming and routine activity of fish.

7. EXISTING GUIDELINES AND STANDARDS

7.1. HUMAN

NIOSH (1978) recommends that occupational exposure to hydrazine be controlled to a level of 0.04 mg/m³ (0.03 ppm), determined on a ceiling concentration in any 2-hour period. This limit is the lowest concentration measureable by the recommended method of analysis with an analytical precision of at least 15%. The ACGIH (1983) currently recommends a TLV-TWA concentration of 0.1 ppm (0.1 mg/m³) for occupational exposure (8-hour workday, 40-hour workweek) to hydrazine. The ACGIH (1983) further gives hydrazine a "skin" designation, indicating that cutaneous absorption may invalidate the TLV, and categorizes hydrazine as a suspect human carcinogen (Appendix A2). A TLV-STEL was not recommended for hydrazine (ACGIH, 1983).

OSHA (1981) has promulgated that occupational exposure to hydrazine be limited to an 8-hour TWA concentration of 1 ppm (1.3 mg/m³). They have also noted that dermal absorption of hydrazine may contribute significantly to total exposure.

7.2. AQUATIC

Guidelines and standards for the protection of aquatic organisms from the toxic effects of hydrazine were not located in the available literature.

8. RISK ASSESSMENT

Numerous studies have demonstrated that orally administered hydrazine, given mainly as hydrazine sulfate, induced high incidences of pulmonary tumors in different strains of mice (see Section 5.1.). The tumors were often multiple and were generally characterized as adenomas and carcinomas. Liver tumors (hepatomas and hepatocellular carcinomas) were also found in some of the orally treated mice that developed lung tumors (see Section 5.1.). Administration of hydrazine sulfate by gavage at a dose of 1.13 mg/day for durations as short as 21-36 weeks produced lung and liver tumors incidences as high as 75-100% and 60-70%, respectively, after lifetime observation (Severi and Biancifiori, 1968; Biancifiori, 1970a,b). Lifetime administration of 0.001% hydrazine (0.069 mg/day) or 0.012% hydrazine sulfate (0.74 mg/day) in the drinking water produced lung tumor incidences of ~50% in Swiss mice (Toth, 1969, 1972a). A multiple dose study in which 0, 0.14, 0.28, 0.56 and 1.13 mg/day hydrazine sulfate was administered by gavage to CBA mice of both sexes indicated that the induction of liver carcinomas was dose-related (Biancifiori, 1970b).

One study is available in which the carcinogenicity of orally administered hydrazine sulfate was evaluated in rats (Severi and Biancifiori, 1968). Daily administration of 18 and 12 mg hydrazine sulfate by gavage for 68 weeks to male and female Cb rats, respectively, produced low incidences of lung adenomas or carcinomas (~21-28%) in both sexes and liver tumors (~31%) in the males.

Hydrazine also elicited increased tumor incidences in rats and mice exposed by inhalation (MacEwen and Vernot, 1980). In this study, notably large groups of animals (100 rats of each sex and 400 female mice) were exposed to 0.05, 0.25, 1.0 and 5.0 (rats only) ppm hydrazine 6 hours/day, 5

days/week for 1 year and were observed for 18 months. As detailed in Table 5-1, increased incidences of tumors were found at the highest concentrations in the male rats (nasal cavity benign epithelial tumors and pituitary adenocarcinoma), female rats (nasal cavity benign epithelial tumors) and female mice (lung adenomas).

The above data provide evidence that hydrazine is carcinogenic in mice and rats following oral and inhalation exposure. Carcinogenicity is better established in the mouse, however, which appears to be the more sensitive species in the oral studies and, therefore, would be the more appropriate species for derivation of an oral carcinogenic potency estimate.

Carcinogenic potency estimates can be derived from the lung tumor response in Swiss mice in the single dose lifetime drinking water study with 0.012% (0.74 mg/day) hydrazine sulfate (Toth, 1969), or from the liver carcinoma response in CBA mice in the multiple dose (0, 0.14, 0.28, 0.56 or 1.13 mg/day) gavage study with hydrazine sulfate (Biancifiori, 1970d). A lifetime drinking water study was also conducted with hydrazine in Swiss mice (Toth, 1972a), but concurrent control data were not provided. The other adequately designed gavage studies with mice were single dose studies with hydrazine sulfate that did not use daily doses lower than those used in the multiple dose gavage study (Biancifiori, 1970d). Using the linearized multistage model adopted by the U.S. EPA (Federal Register, 1980) carcinogenic potency factors (q_1^*) of 0.910 and 2.96 $(mg/kg/day)^{-1}$ can be derived for humans from the tumor response in the male mice in the single dose lifetime drinking water study (Toth, 1969) and the shorter-term multiple dose gavage study (Biancifiori, 1970d), respectively. The conversion factor used in the calculation of these q_1^* values for humans from animal data was the cube root of the body weight ratio (Federal Register, 1980)

which has been demonstrated empirically to adjust for species to species extrapolation. Data used in the derivation of this q_1^* value are presented in Appendices II and III. It should be pointed out that the q_1^* values are for hydrazine sulfate. The values for hydrazine alone would be expected to be less based on molecular weight of the molecule.

In this document, two drinking water studies for hydrazine sulfate have been used to calculate the carcinogenic potency q_1^*. Although it is likely that hydrazine is responsible for the tumoregenic response in these experiments, the potency calculated on the basis of this compound may not be appropriate for the hydrazine itself, even after converting the dose rate from hydrazine sulfate to hydrazine because absorption rates in the body likely differ between the two compounds. Therefore, the study on hydrazine (e.g., Toth, 1972a) is used to estimate the carcinogenic potency for hydrazine.

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Yamamoto, R.S. and J.H. Weisburger. 1970. Failure of arginine glutamate to inhibit lung tumour formation by isoniazid and hydrazine in mice. Life Sci. 9: 285. (Cited in IARC, 1973)

APPENDIX A

LITERATURE SEARCHED

This profile is based on data identified by computerized literature searches of:

CA SEARCH (Files 308, 309, 310, 311, 320)
TOXLINE
MEDLINE
RTECS
SCI SEARCH
OHM TADS
STORET
SRC Environmental Fate Data Bases
SANSS
AQUIRE

These searches were conducted in June and December, 1983. In addition, hand searches were made of Chemical Abstracts (Collective Indices 6 and 7th), and the following secondary sources were reviewed:

ACGIH (American Conference of Governmental Industrial Hygienists). 1980. Documentation of the Threshold Limit Values, 4th ed. (Includes Supplemental Documentation, 1981, 1982, 1983). Cincinnati, OH. 486 p.

ACGIH (American Conference of Governmental Industrial Hygienists). 1983. TLVs: Threshold Limit Values for Chemical Substances and Physical Agents in the Workroom Environment with Intended Changes for 1983-84. Cincinnati, OH. 94 p.

BCPC (British Crop Protection Council). 1977. Pesticide Manual, 5th ed., H. Martin and C.R. Worthing, Ed. British Crop Protection Council. 593 p.

Clayton, G.D. and F.E. Clayton, Ed. 1981. Patty's Industrial Hygiene and Toxicology, 3rd rev. ed., Vol. 2A. John Wiley and Sons, NY. 2878 p.

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Grayson, M. and D. Eckroth, Ed. 1978-83. Kirk-Othmer Encyclopedia of Chemical Technology, 3rd ed. John Wiley and Sons, NY. 23 Vol.

Hamilton, A. and H.L. Hardy. 1974. Industrial Toxicology, 3rd ed. Publishing Sciences Group, Inc., MA. 575 p.

ITII (International Technical Information Institute). 1982. Toxic and Hazardous Industrial Chemicals Safety Manual for Handling and Disposal with Toxicity and Hazard Data. ITII, Tokyo, Japan. 700 p.

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U.S. EPA. 1983. CHIB Existing Chemical Assessment Tracking System. Name and CAS Number Ordered Indexes. Office of Toxic Substances, Washington, DC.

USITC (United States International Trade Commission). 1983. Synthetic Organic Chemicals. U.S. Production and Sales, 1982. Washington, DC. USITC Publ. 1422.

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APPENDIX B

CANCER DATA SHEET FOR DERIVATION OF q_1^*

Compound: Hydrazine sulfate

Reference: Toth, 1969

Species, Strain, Sex: Mouse, Swiss, male

Body Weight: 0.032 kg (measured)

Length of Exposure (l_e) = 588 days

Length of Experiment (L_e) = 588 days

Lifespan of Animal (L) = 728 days

Tumor Site and Type: lung adenoma or carcinoma

Route, Vehicle: drinking water

Experimental Doses or Exposures	Transformed Dose mg/kg/day	Incidence No. Responding/ No. Tested (or Examined)
0 mg/day	0 mg/kg/day	11/110
0.74 mg/day (reported average daily consumption)	23.1 mg/kg/day	25/50

Unadjusted q_1^* from study = 3.6923×10^{-2} $(mg/kg/day)^{-1}$

Human q_1^* = 9.0966×10^{-1} $(mg/kg/day)^{-1}$

APPENDIX C

CANCER DATA SHEET FOR DERIVATION OF q_1^*

Compound: Hydrazine sulfate

Reference: Biancifiori, 1970d

Species, Strain, Sex: Mouse, CBA/Cb/Se, male

Body Weight: 0.03 kg (assumed)

Length of Exposure (l_e) = 175 days

Length of Experiment (L_e)[a] =

0	21	42	84	170	(mg/25 weeks)
700	686	588	546	609	(days)

Lifespan of Animal (L) = 730 days

Tumor Site and Type: liver hepatomas

Route, Vehicle: gavage, water

Experimental Doses or Exposures	Transformed Dose mg/kg/day	Incidence No. Responding/ No. Tested (or Examined)
0 mg/25 weeks	0	3/30
21	1.02	1/26
42	2.38	7/25
84	5.13	12/25
170	9.3	15/25

Unadjusted q_1^* from study = 1.2826×10^{-1} $(mg/kg/day)^{-1}$

Human q_1^* = 2.9591 $(mg/kg/day)^{-1}$

[a]Le was determined as the mean of the lengths of exposure for all treatment groups, 607 days, when used to calculate the human q_1^*.